REMARKS

Prior to entry of the instant amendment, claims 1, 3, 4, 19, 21, 22, 27, 33-36, 39-63 and 84-108 were pending in the application, and claims 19, 21, 22, 27, 34-36, 40-63, 91-108 were pending and withdrawn. Claims 1, 86 and 87 have been amended. Therefore, upon entry of the presently amended claim set, claims 1, 3, 4, 19, 21, 22, 27, 33-36, 39-63 and 84-108 are pending, and claims 19, 21, 22, 27, 34-36, 40-63, 91-108 are pending and withdrawn.

Claim 1 has been amended to include the limitation that the siRNA comprises a cleavage site for RISC, and that at least one adenosine nucleotide located within 2 nucleotides upstream and 9 nucleotides downstream of the cleavage site referencing the antisense strand is substituted with a 2'-deoxy adenosine nucleotide, and that at least one guanosine nucleotide located within 2 nucleotides upstream and 9 nucleotides downstream of the cleavage site referencing the antisense strand is substituted with a 2'-deoxy guanosine nucleotide. Support for this amendment can be found, at least, for example, in Figure 13 of the application as filed.

Claim 1 has also been amended to specify that the antisense strand comprises uridines, cytidines, adenosines and guanosines. Support for this amendment can be found throughout the specification, claims and figures as originally filed.

Claim 86 has been amended to specify that the antisense strand is modified by the substitution of at least one adenosine with a 2'-deoxy adenosine and at least one guanosine with a 2'-deoxy guanosine located within 2 nucleotides upstream and 9 nucleotides downstream of the cleavage site referencing the antisense strand.

Claim 87 has been amended to specify that the antisense strand is modified by the substitution of each adenosine with a 2'-deoxy adenosine and each guanosine with a 2'-deoxy guanosine located within 2 nucleotides upstream and 9 nucleotides downstream of the cleavage site referencing the antisense strand.

Support for the limitations of amended claims 86 and 87 can be found at least, for example, in Example 10, Figure 10A, Example 13, Figure 19 and Figures 13A, B and C. No new matter has been added.

The foregoing claim amendments have been made solely for the purpose of expediting prosecution of the present application and should in no way be construed as acquiescence to any of the Examiner's rejections in this or in any other Office Action issued in the present application. Applicant reserves the right to pursue the subject matter of the present claims prior to being amended herein in this application or in another related application.

In view of the foregoing claim amendments and the arguments set forth below, Applicant respectfully submits that the claims are now in condition for allowance.

Rejection of Claims 1, 3-4, 33, 39 and 84-90 Under 35 USC §112

Claims 1, 3-4, 33, 39 and 84-90 have been rejected under 35 USC §112. The Examiner states that "[t]he specification does not [provide] adequate written description for the entire genus comprising siRNA targeted to any target gene comprising any number of modified nucleotides that are capable of inhibiting the expression of said target gene by at least 30%," and asserts that "one of skill in the art would not know which sequence… would provide the necessary activity of silencing gene expression by at least 30%."

Applicant respectfully disagrees. Compounds of the invention are RNA molecules that exhibit high levels of complementarity to their target mRNA, and the instant application teaches in (page 41, lines 3-18) that said compounds can be designed to target any gene of known sequence by "[b]eginning with the AUG start codon, look for AA dinucleotide sequences; each AA and the 3' adjacent 16 or more nucleotides are potential siRNA target." The instant application teaches production and purification of RNA (pages 34-35), and teaches efficacy assays (pages 30-32). Based on the teachings of the instant application, one of ordinary skill in the art would be able to choose a target gene, determine the appropriate siRNA compositions, and conduct the routine assays in order to identify those meeting the functional limitation of silencing gene expression by at least 30%.

Applicant, therefore, respectfully requests that the rejection of claims 51, 3-4, 33, 39 and 84-90 under 35 USC §112 be reconsidered and withdrawn.

Rejection of Claims 21, 3-4, 33, 39 and 84-90 USC §103(a)

Claims 1, 3-4, 33, 39 and 84-90 have been rejected under 35 USC §103(b) as being unpatentable over Fosnaugh et al. (US2003/0143732). The Examiner takes the position that it would have been obvious to one of ordinary skill in the art to "synthesize a siRNA comprising chemically modified nucleotides as taught [by Fosnaugh] and optimize the incorporation of said modifications to obtain a siRNA with the highest ability to inhibit the desired gene expression."

Applicant respectfully disagrees. However, solely to expedite prosecution, claim 1, as amended, is drawn to a small interfering RNA (siRNA), comprising a sense strand and an antisense strand, wherein the antisense strand is complementary to the sense strand and has a

sequence sufficiently complementary to a target mRNA sequence to direct target-specific RNA interference (RNAi), and wherein the target mRNA sequence comprises a cleavage site for RISC, wherein the antisense strand comprises uridines, cytidines, adenosines and guanosines with at least one adenosine or guanosine within 2 nucleotides upstream and 9 nucleotides downstream of the cleavage site referencing the antisense strand, and wherein the antisense strand is modified by the substitution of each uridine with a 2'-fluoro uridine and each cytidine with a 2'-fluoro cytidine and is modified by the substitution of at least one adenosine with 2'deoxy adenosine or at least one guanosine with 2'-deoxy guanosine within the 2 nucleotides upstream and 9 nucleotides downstream of the cleavage site, such that *in vivo* stability is enhanced as compared to a corresponding unmodified siRNA, and wherein the siRNA retains the ability to inhibit expression of the target mRNA by at least 30%.

The siRNA compounds of amended claim 1 comprise antisense strands featuring 2'-fluoro modifications on all pyrimidine nucleobases, and 2'-deoxy modifications on purine nucleobases located within the above-identified region.

Fosnaugh does not teach such modifications. Fosnaugh's recitation of nucleotide modifications of the antisense strand [0052, 0053] is exemplified in the specification only by pyrimidine nucleobases comprising 2'-fluoro, 2'-OMe, and in a limited instance (thymidine in the overhang region) 2'-deoxy modifications (see [0145, 0146]; Figures 4 and 5). Fosnaugh has no examples of purine modifications in general, nor does it particularly disclose 2'-deoxy modifications of purine nucleobases. Furthermore, Fosnaugh teaches away from the use of 2'-deoxy modifications at internal positions by limiting its own use to thymidine residues in the terminal, overhang regions. As such, this reference fails to teach or suggest siRNA compounds comprising antisense strand 2'-fluoro pyrimidine and 2'-deoxy purine modifications, and one of ordinary skill in the art would not have been motivated, nor have a reasonable expectation of success, to pursue this approach.

In contrast, the instant invention teaches specific modifications to specific nucleotide residues (*i.e.*, 2'-fluoro pyrimidines and 2'-deoxy purines) that confer increased bioavailability and *in vivo* stability relative to the unmodified variant, while preserving the ability to direct target-specific RNA interference. The Examiner is referred to Figure 13B of the application as filed. Columns 6, 11, 20, 29 and 38 depict the relative expression levels within HeLa cells treated with: *i*) unmodified siRNA, *ii*) antisense strand (AS) 2'-deoxy siRNA, *iii*) AS 2'-fluoro pyrimidine siRNA, *iv*) AS 2'-fluoro pyrimidine siRNA with 2'-

deoxy purines at positions 9, 10 and 13, and *v*) AS 2'-fluoro pyrimidine siRNA with 2'-deoxy purines at positions 9-19. Comparing columns 20 and 29, it is clear that the combination of specific pyrimidine modifications with specific purine modifications affords an advantage, in terms of expression inhibition, over pyrimidine modifications alone. This trend is found again in the comparison of columns 29 and 38, wherein increasing the modified purine content further decreases the expression level. The instant application clearly sets forth an unexpected and nonobvious phenomena observed under the specific conditions described above. Applicant teaches that:

> [i]n general, mixing 2'-fluoro modification with deoxy modification could rescue siRNA function (Figure 13B, lanes 25-60). When 2' FU, FC nucleotides were incorporated into the EGFP siRNA antisense strand with guanine and adenine deoxynucleotides at positions 9, 10 and 13, which base pair with nucleotides lining the cleavage site, (Figure 13A), EGFP RNAi effects were almost indistinguishable from wild type levels (Figure 13B, lanes 25-33; Table 1, row 5).

Thus, the ordinary skilled artisan could not possibly have predicted with any expectation of success, prior to Applicant's invention, that an siRNA comprising a combination of 2'-fluoro pyrimidines and 2'-deoxy purines, present to the extent and at the specific positions required by the instant claims, would surprisingly retain the ability to mediate RNAi.

Applicant, therefore, respectfully requests reconsideration and withdrawal of the rejection of claims 1, 3-4, 33, 39 and 84-90 under 35 USC §103(b).

CONCLUSION

In view of the foregoing, entry of the amendments and remarks herein, reconsideration and withdrawal of all rejections, and allowance of the instant application with all pending claims are respectfully solicited. If there are any questions regarding the proposed amendments to the application, we invite the Examiner to call Applicant's representative at the telephone number below.

An extension of time and appropriate fee is being filed herewith. If any additional fees are due, please charge our Deposit Account No. 12-0080, under Order No. UMY-062RCE from which the undersigned is authorized to draw.

Dated: August 12, 2009

Respectfully submitted,

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